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Glucose toxicity: the implications of hyperglycemia in the pathophysiology of diabetes mellitus

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Abstract

Non-insulin-dependent diabetes mellitus (NIDDM) results from a disruption of normal glucose homeostasis, primarily insulin secretion and hepatic and peripheral insulin action. However, chronic hyperglycemia has been shown in animal models to contribute to impaired insulin secretion as well as to peripheral insulin resistance. Consequently, stringent control measures aimed at ameliorating chronically elevated blood glucose levels may help lessen the cellular "toxic" effect of hyperglycemia.

Résumé

Le diabète non-insulino-dépendant résulte d'une disruption de l'homéostase du glucose, de la sécrétion d'insuline, et de l'action périphérique et hépatique de cette hormone. Cependant, l'hyperglycémie chronique a bien été démontrée chez des modèles animaux créant une diminution de la sécrétion d'insuline ainsi qu'une résistance périphérique à l'insuline. Par conséquent, des mesures de contrôle stricte visant l'amélioration de l'hyperglycémie pourraient réduire l'effet toxique de l'hyperglycémie.

Introduction

As a result of substantial evidence linking hyperglycemia to the development and progression of complications associated with diabetes [1-7], thera-

peutic strategies are currently focused on rigorously controlling elevations in blood glucose which exist in diabetes. Chronic hyperglycemia has been correlated with the microvascular complications of diabetes such as nephropathy, neuropathy, and retinopathy, as well as macrovascular disease, protein glycation, and impaired cellular immunity [8-10]. Recently, it has been demonstrated that strict glycemic control can prevent or delay the development of some of these complications [2, 11]. While these studies, utilizing incremental insulin therapy, were done with patients with insulin-dependent diabetes mellitus (IDDM), there is a strong supposition that the findings may be applied to patients with non-insulin-dependent diabetes mellitus (NIDDM) [12].

In the past decade, a wealth of specific data on the cellular and molecular actions of insulin has established that chronic hyperglycemia impairs the secretion of insulin and contributes to insulin resistance – a phenomenon known as glucose toxicity. That NIDDM appears in diverse groups of patients, sharing remarkably similar metabolic features despite diverse genetic backgrounds, suggests that a common biochemical mechanism may be responsible for several aspects of this syndrome. Several studies, however, have demonstrated that in certain populations, NIDDM may result from an inherited defect. While the exact type of defect remains unknown, its phenotype is characterized by insulin resistance involving the non-oxidative pathway of glucose metabolism [13], but is not a result of a genetic defect in the expression of the insulin-

responsive glucose transporter gene (GLUT-4) in human skeletal muscle [14].

While different theories may exist for the development of NIDDM, there is a consensus about what characterizes the condition once it is established: fasting hyperglycemia resulting from a defect in insulin secretion as well as an alteration of insulin response. Consequently, chronic hyperglycemia, through a down-regulation of the glucose transport system, may result in cellular desensitization throughout the body. At the level of muscle and adipose cells, this would be reflected by a defect in insulin action, while at the level of the β -cell, impairment in insulin secretion would be apparent.

Hyperglycemia and insulin secretion

To evaluate the effect of chronic hyperglycemia on insulin secretion, an animal model of NIDDM was developed. Fasting plasma glucose levels were measured in partially pancreatectomized rats; these levels, which closely resemble insulinopenic NIDDM, were compared with those of a control group and a pancreatectomized group given the renal tubular glucose transport inhibitor, phloridzin, to control plasma glucose [15]. Phloridzin resulted in complete normalization of the glucose profile with no change in plasma insulin levels.

Further, to examine the effects of glycemic control on insulin secretion, a hyperglycemic clamp was used. The typical biphasic pattern of insulin secretion was seen in the control rats, while in the partially pancreatectomized rats the first phase was lost and the second phase was markedly impaired. In the phloridzin-treated partially pancreatectomized rats, in which hyperglycemia was controlled, both phases of insulin secretion were significantly enhanced compared with the hyperglycemic group. While insulin secretion in the phloridzin-treated group did not rise to the level of the control group because of the partial pancreatectomy, the 2 groups were similar when insulin response was compared per gram of pancreatic tissue (Fig. 1). Additionally, the effect of arginine, a non-glucose insulin secretagogue, on the β -cell was investigated in these hyperglycemic rats. Plasma insulin response to arginine was increased 3-fold in the pancreatectomized rats but returned to normal when the hyperglycemia was corrected with phloridzin.

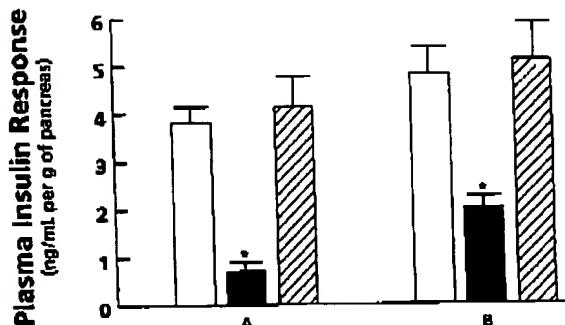


FIG. 1. Mean plasma insulin responses per gram of pancreatic tissue during a +5.6 mM clamp study. Sham-operated controls are open bars, 90% pancreatectomized rats are solid bars, and phloridzin-treated pancreatectomized rats are hatched bars. * $p < 0.01$ vs. controls. Reproduced from *The Journal of Clinical Investigation*, 79: 1037–44, 1987, by copyright permission of The American Society for Clinical Investigation [15].

These results clearly demonstrate that the impaired β -cell response is functional and not a result of β -cell death, and that chronic hyperglycemia in rats produces an impaired response to acute glucose stimulus in pancreatic tissue. Moreover, the abnormalities of insulin secretion caused by hyperglycemia can be reversed when it is corrected [15].

The improvement in insulin secretion that follows control of hyperglycemia was seen clinically following various maneuvers that lower plasma glucose concentration. Kosaka et al. measured insulin secretion in patients with moderately severe fasting hyperglycemia (>11.1 mmol/L) who were assigned to 3 groups: weight loss, exogenous insulin, or a sulfonylurea [16]. Insulin secretion increased significantly in all 3 therapy groups regardless of the method of plasma glucose reduction (Fig. 2). It is notable that these 3 treatments vary in their expected effect on insulin secretion, with weight reduction being neutral, insulin being inhibitory, and sulfonylurea being a stimulant. The improvement in insulin secretion in all 3 groups would point to the reduction in glucose toxicity as the means of increasing responsiveness of the β -cell to glucose.

The mechanism by which hyperglycemia reduces insulin secretion is less well understood. A general down-regulation of glucose transport and metabolism in all body cells has been suggested [17], and

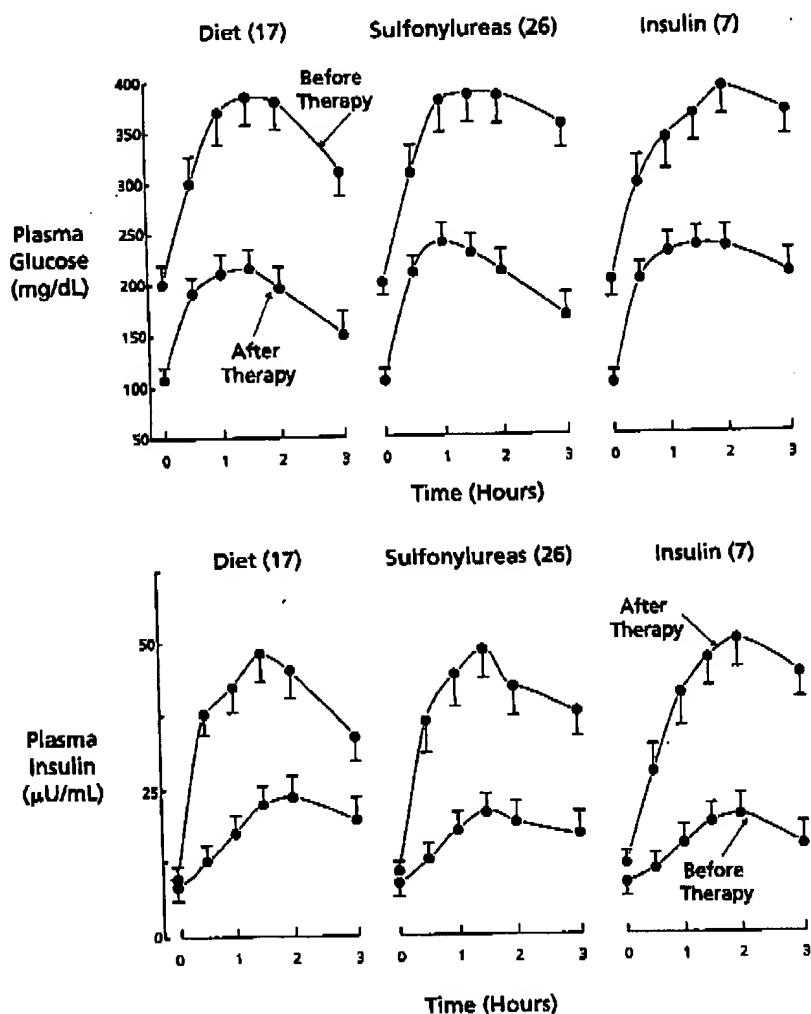


FIG. 2. Effects on plasma glucose concentration (A) and insulin secretion (B) after an oral glucose tolerance test in patients treated with diet, or sulfonylurea, or insulin. Treatment effects for both plasma glucose and plasma insulin are significant at the $p < 0.01$ level. Reproduced with permission. KOSAKA K, KUZUYA T, AKANUMA Y, HAGURA R: Increase in the insulin response after treatment of overt maturity-onset diabetes is independent of the mode of treatment. *Diabetologia* 18: 23-8, 1980. © Springer-Verlag [16].

quite a number of possible mechanisms have been examined. To summarize, it would appear that the decrease in insulin secretion is not due to changes in intracellular glucose metabolism or insulin synthesis, but that the coupling of glucose metabolism to the secretory process is desensitized [17]. There is evidence that phosphoinositol metabolism and the activation of C-kinases play a primary role in the

regulation of insulin release, and that these processes may be sensitive to chronic intracellular hyperglycemia [18, 19].

In man, then, insulin secretion in response to glucose declines over time as NIDDM progresses and fasting plasma glucose levels increase. At very slight initial elevations of plasma glucose, insulin levels rise in response to glucose challenge, but, as

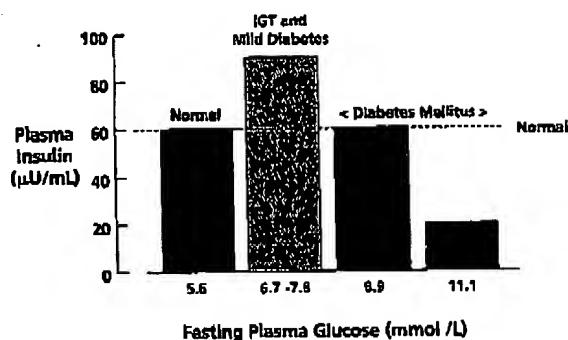


FIG. 3. Insulin secretion in response to rising fasting plasma glucose levels. Reproduced with permission. UNGER RH, GRUNDY S: Hyperglycemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. *Diabetologia* 28: 119-21, 1985. © Springer-Verlag [20].

shown in Fig. 3, this response declines as fasting plasma glucose rises above 7.8 mmol/L, and is markedly reduced at 11.1 mmol/L.

The accumulated findings to date argue strongly that this phenomenon is due to glucose toxicity, a direct effect of hyperglycemia on the β -cell, and that hyperglycemia, as well as being a marker of diabetes, contributes to the pathophysiology and progression of NIDDM.

Hyperglycemia and insulin resistance

Insulin resistance is characteristic of both IDDM and NIDDM, although the resistance comes about by different means, with the defect being acquired in IDDM and presumably inherited in NIDDM. Unger and Grundy first proposed the role of hyperglycemia in the impairment of insulin-mediated glucose disposal [20]. This was confirmed in an experiment, again utilizing the above-described animal model of NIDDM [21]. Partially pancreatectomized phloridzin-induced diabetic rats were randomized to continue or discontinue phloridzin treatment. Euglycemic insulin-clamp studies were performed to assess the effect of chronic hyperglycemia and euglycemia on insulin sensitivity. Results showed that plasma glucose levels were inversely proportional to the degree of muscle glucose uptake defect, demonstrating the correlation between the severity of hyperglycemia and the severity of insulin

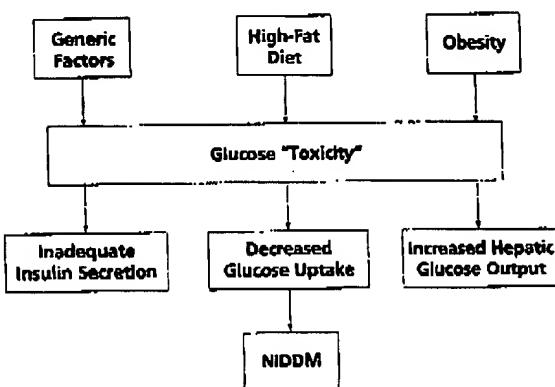


FIG. 4. Intracellular glucose toxicity is a primary factor in the development of NIDDM.

resistance present in muscle. Furthermore, to investigate the possibility that insulin resistance results from a defect in the glucose transport system, muscle glucose-6-phosphate levels were measured. If the hyperglycemia-induced defect in insulin action resulted from an effect on glucose transport or phosphorylation, treatment with phloridzin would be expected to increase cellular influx of glucose-6-phosphate. Conversely, a defect in the intracellular apparatus, such as glycogen synthesis, would result in decreased levels. The results demonstrated that in response to an insulin challenge, phloridzin-treated rats exhibited significantly higher levels of glucose-6-phosphate compared with untreated diabetic rats, suggesting that an improvement in glucose transport or phosphorylation had occurred.

The effect of insulin on glucose transport is predominantly mediated by the translocation of GLUT-4. As insulin stimulates this effect, vesicle translocation occurs in the plasma membrane, facilitating the input of glucose to insulin-sensitive cells. Consequently, while not genetic in origin, the muscle cell defect may be an alteration of GLUT-4 function.

It has been demonstrated experimentally that chronic hyperglycemia is capable, in fact, of inducing insulin resistance. Correction of chronic hyperglycemia accomplishes a reversal of the peripheral insulin resistance by up-regulation of the glucose transport system. This phenomenon takes place in the absence of any alteration in glucose transporter number or mRNA [22]. Genetic factors in any of

the pathways of glucose utilization, or an increase in fat, may mediate glucose resistance at the cellular level.

This reduction in insulin resistance by controlling hyperglycemia represents a second clinically important consideration for treatment, and a further aspect of glucose toxicity as part of the overall pathophysiology of NIDDM (Fig. 4). A prolonged increase in intracellular glucose toxicity producing resistance, plus the hyperglycemia-induced impairment of insulin secretion, constitute the overall effects of glucose toxicity and represent the basis for better metabolic control.

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Clin Invest Med Vol. 18, 1995

Key words: hyperglycemia, glucosamine, insulin resistance, insulin secretion, glycogen synthesis, glucose uptake

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Received 11 October 1993

Mechanisms of pancreatic B-cell dysfunction and glucose toxicity in non-insulin-dependent diabetes

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Introduction

The insulin response to food ingestion is determined by the direct actions of glucose and certain amino acids on the pancreatic B-cell together with indirect actions generated through activation of both hormonal and neural arms of the enteroinsular axis [1-3]. These signals are normally integrated at the level of the pancreatic B-cell such that insulin is secreted to appropriately regulate nutrient metabolism and glucose homeostasis. In non-insulin-dependent diabetes mellitus (NIDDM), defects in the mechanisms that regulate insulin secretion make a major contribution to the glucose intolerance and metabolic disarray associated with the disease [4-6]. Possible molecular mechanisms underlying pancreatic B-cell dysfunction in NIDDM include site-specific defects in the stimulus-secretion coupling pathway and changes in B-cell function consequent to alterations in external influences on the B-cell. The participation and interaction of the various pathways to disturbances of insulin secretion in NIDDM are considered below in the framework of our present understanding of the regulation of B-cell function and stimulus-secretion coupling.

Susceptible points in B-cell stimulus-secretion coupling

Glucose insensitivity of the pancreatic B-cell lies at the heart of defective insulin secretion in NIDDM [4-6]. Glucose is the principal regulator of B-cell function and also amplifies the insulinotropic actions of all other secretagogues, including entero-

insular hormones and neurotransmitters [7]. It follows that each site in the series of steps linking B-cell glucose recognition to insulin discharge represents a potential influential lesion that might result in defective insulin secretion, characteristic of NIDDM. The normal secretory pathway induced by glucose starts with transport of the sugar into the B-cell by the GLUT2 glucose transporter (for comprehensive coverage of the pathway see [8-11]). Phosphorylation of glucose, by glucokinase, and subsequent metabolism leads to the generation of ATP and increase of the ATP/ADP ratio. This results in closure of ATP-sensitive K⁺ channels (K⁺-ATP channels) in the B-cell membrane, depolarization, opening of voltage-dependent Ca²⁺ channels and Ca²⁺ influx. The resulting increase in cytoplasmic Ca²⁺ concentration ([Ca²⁺]_i) then triggers the secretory machinery, culminating in the discharge of insulin by exocytosis. Ca²⁺ also activates enzymes such as adenylyl cyclase (with generation of cyclic AMP) and phospholipase C (with production of inositol 1,4,5-trisphosphate and diacylglycerol, which activates protein kinase C) that serve both to displace Ca²⁺ from intracellular stores and to sensitize the secretory machinery to [Ca²⁺]_i [10]. Hormonal and neural elements of the enteroinsular axis potentiate the insulin secretory process through interactions with membrane receptors that are also linked to activation of adenylyl cyclase or phospholipase C [7].

Site-specific defects in B-cell dysfunction

Site-specific defects in the pancreatic B-cell have been uncovered in studies evaluating mechanisms of defective insulin secretion using islets isolated from various animal models of NIDDM [6]. Less

Abbreviations used: NIDDM, non-insulin-dependent diabetes mellitus; [Ca²⁺]_i, cytoplasmic Ca²⁺ concentration; K⁺-ATP, ATP-sensitive K⁺ channel.

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certain is the extent to which such defects (summarized in Table 1) are primary genetic manifestations or secondary features acquired from abnormalities of the B-cell environment and external influences. A future search for mutations of key functional proteins in the B-cell secretory machinery will undoubtedly help to address this issue. These discussions have an important bearing on the debate, conducted elsewhere, on whether the primary defect in NIDDM is at the level of the B-cell rather than at the site of insulin action [4, 5, 12].

Insulin synthesis and trafficking

Point mutations of the insulin gene and other mutations which may affect the intracellular processing and trafficking of proinsulin have been observed in small numbers of human subjects [13]. Although the frequency of such mutations is low, mechanisms which potentially lead to the abnormal release of proinsulin from the B-cell are relevant to the hyperproinsulinaemia encountered in NIDDM.

Stimulus-secretion coupling

Abnormalities have been detected in NIDDM at almost all known stages of the pancreatic B-cell stimulus-secretion coupling pathway [6]. Brief consideration of the principal site-specific lesions contributing to defective insulin secretion in specific examples of NIDDM is given below.

GLUT2 glucose transporter

A variable reduction in expression of the B-cell GLUT2 glucose transporter has been recorded in human NIDDM and several animal models with diabetes [8, 14]. A reversible loss of GLUT2 expression has been reported in *db/db* mice on an undefined background genome [15]. However, since glucose transport is not normally rate limiting

in B-cell glucose metabolism [8], abnormalities of GLUT2 seem to be generally less important than defects that affect more distal steps in the insulin secretory pathway.

Glucokinase

An alteration of glucokinase can be expected to disturb insulin secretion by virtue of the role of the enzyme in determining the rate of signal generating metabolic flux in the B-cell [8]. Most notable in this context is the detection of functionally significant mutations of the glucokinase gene in a high proportion of MODY (maturity-onset diabetes of the young) patients with defective insulin secretion [16]. Mutations at this locus are not common in classical NIDDM [17]. However, the apparent link between glucokinase activity and defective insulin secretion highlights the need for more detailed studies on possible changes in the activity of the enzyme in the diabetic B-cell.

Glucose-6-phosphatase (glucose cycle)

A high rate of glucose cycling (namely metabolism of glucose to glucose-6-phosphate and back to glucose) catalysed by glucokinase and glucose-6-phosphatase has been demonstrated in the islets of *ob/ob* mice, GK rats and rats treated with streptozotocin during the neonatal period [18]. Consumption of one molecule of ATP for each molecule of glucose cycled might, by decreasing the ATP pool, interfere with the regulation of K⁺-ATP channels and contribute to defective insulin secretion.

Mitochondrial FAD-glycerophosphate dehydrogenase

Activation of mitochondrial FAD-linked glycerophosphate dehydrogenase by [Ca²⁺]_i is proposed to optimize ATP generation from glucose in B-cells

Table 1
Possible mechanisms involved in pancreatic B-cell dysfunction in NIDDM

Site-specific defects	Alterations of external input
Insulin synthesis and trafficking	Glucose toxicity
GLUT2 glucose transporter	B-cell hyperactivity
Glucokinase	Cellular environment
Glucose-6-phosphatase	Islet vasculature
FAD-glycerophosphate dehydrogenase	Local modulators
Generation of ATP	Autonomic tone
K ⁺ -ATP channels	Circulating nutrients and hormones
[Ca ²⁺] _i and contractile proteins	

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through preferential stimulation of oxidative, as opposed to total, glycolysis [19]. The enzyme appears therefore to serve an important role in the glucose-sensing function in the B-cell. Alterations of mitochondrial FAD-linked glycerophosphate dehydrogenase activity have been described in various animal models of experimentally-induced and spontaneous NIDDM, including adult rats treated neonatally with streptozotocin, GK rats, *fa/fa* rats and C57BL/KsJ *db/db* mice [20].

Generation of ATP

Despite the key role of ATP generation and increase of ATP/ADP ratio in the closure of K⁺-ATP channels, few studies have actually addressed directly the link between defective insulin secretion and perturbations of ATP generation. One problem is undoubtedly the difficulty in monitoring functionally important changes of ATP specifically adjacent to K⁺-ATP channels. Nevertheless, a compromise in the generation of cellular ATP has been clearly shown to be associated with the glucose unresponsiveness of fetal rat pancreatic B-cells [21].

K⁺-ATP channels

Early studies of pancreatic B-cell membrane potential and ⁸⁶Rb efflux, from preloaded islets of C57BL/KsJ *db/db* mice and diabetic Chinese hamsters, demonstrated an association between abnormalities in the regulation of K⁺ permeability and defective insulin secretion [22-24]. Cell-attached and inside-out configurations of the patch-clamp technique have been used recently to directly assess the regulation of K⁺-ATP channels in B-cells isolated from animal models. Studies using the neonatal-streptozotocin-treated rat model and GK rats indicate that the inhibitory effect of glucose on B-cell K⁺-ATP channels is impaired in NIDDM [25, 26]. However, sensitivity of the channels to direct application of ATP using inside-out patches was intact. This suggests that glucose insensitivity of the K⁺-ATP channels in these models reflects impaired cellular ATP generation rather than a defect in the K⁺-ATP channel *per se*.

Regulation of [Ca²⁺]_i and contractile proteins

Disturbances in the regulation of transmembrane Ca²⁺ fluxes and [Ca²⁺]_i represent a common feature associated with defective insulin secretion in animal models of NIDDM, including C57BL/KsJ *db/db* mice, Spiny mice and neonatal-streptozotocin-treated rats [6]. Abnormal regulation of [Ca²⁺]_i undoubtedly plays a major role in the defec-

tive stimulus-secretion of the B-cell in NIDDM. However, the extent to which such abnormalities reflect disturbances at earlier stages of the secretory process is uncertain. Site-specific lesions in voltage-dependent Ca²⁺ channels, intracellular Ca²⁺ transport and the effects of Ca²⁺ on the exocytic machinery remain to be established. Apparent disturbances in microtubules and microfilaments involved in exocytosis have been reported in diabetic Spiny mice and C57BL/KsJ *db/db* mice [27, 28].

Alterations of external input and B-cell dysfunction

NIDDM is associated with significant disturbances in the local environment of the B-cell, including profound changes in the concentrations of nutrients and hormones with established effects on insulin secretion [4-6]. As illustrated by specific examples given below, such alterations can undoubtedly contribute to B-cell dysfunction. In certain cases, most notably hyperglycaemia-induced glucose toxicity, alterations in external environment may actually lead to the production of site-specific defects in the B-cell.

Local modulators of secretion

Disturbances in location and relative proportions of the various islet cell types are commonly observed in diabetes [29]. Such alterations undoubtedly disrupt the normal functional interactions between B-cells and the surrounding A- and D-cells [30]. Local paracrine effects and actions of glucagon and somatostatin dependent on normal vascular flow through the islets may be affected. However, possibly more important are changes in the secretion and action of a large number of other proposed local modulators of insulin secretion [3, 7, 31]. These include biogenic amines, pancreastatin, islet amyloid polypeptide (IAPP), opiate peptides, thyrotropin-releasing hormone, corticotropin-releasing factor, peptide YY, atrial natriuretic peptide, diazepam-binding inhibitor and other less well-known peptides. Pancreastatin and IAPP, which are released from the B-cell, have been proposed to contribute to B-cell dysfunction through inhibition of insulin secretion [7, 32, 33].

Alterations of autonomic tone

The islet autonomic innervation plays a subtle and possibly important role in the fine-tuning of insulin secretion [3, 34]. Alterations of autonomic tone undoubtedly occur in NIDDM, as illustrated by the well-known deleterious effect of hyperglycaemia on

nerve conduction velocity [35]. The B-cell innervation may be also disrupted in diabetes as illustrated by ultrastructural observations in diabetic Spiny mice and Chinese hamsters [36, 37] and by alterations in the levels of neuropeptides in the islets of various diabetic models [38]. Classical and peptidergic neurotransmitters include acetylcholine, noradrenaline, cholecystokinin, somatostatin, galanin, gastrin-releasing peptide, vasoactive intestinal polypeptide and neuropeptide Y [3, 7, 34]. Alterations in the actions of these neurotransmitters in diabetes may contribute to the amplification or suppression of insulin secretion through parasympathetic and sympathetic nerves, respectively.

B-cell hyperactivity

There is good evidence for a link between B-cell hyperactivity and defective insulin responses in some forms of experimental and spontaneous diabetes [6]. Thus in various animal models of NIDDM, loss of an insulin response to glucose shows a close association with the extent of hyperinsulinaemia [6]. Interventions such as fasting in *ob/ob* mice, which decreases the extent of hyperinsulinaemia and hyperglycaemia, have also been reported to improve insulin secretory responsiveness [39]. Defective insulin secretion in glucose-infused rats may also partly result from induction of B-cell hyperactivity in addition to possible direct deleterious effects of the accompanying hyperglycaemia [40, 41]. Such observations suggest that hyperinsulinaemia, arising from excessive B-cell stimulation by overactive entero-insular axis, contributes to defective insulin secretion in many susceptible animal syndromes of NIDDM [38].

Glucose toxicity

Studies in man and experimental animals, using cultured islets, both *in vivo* and *in vitro*, indicate that long-term exposure to a hyperglycaemic environment results in a gradual impairment of insulin secretion [5, 42]. Such observations have reaffirmed the concept of glucose toxicity and the view of hyperglycaemia as an inducer, as well as a consequence of B-cell dysfunction [43]. Pancreatic B-cell glucose toxicity is particularly well illustrated by the induction of defective insulin secretion in rats subjected to partial pancreatectomy or to glucose infusions [5, 6, 42]. Interestingly, there seems to be significant species and strain variability in susceptibility to the deleterious actions of hyperglycaemic culture conditions on the function of isolated islets. The B-cells of certain strains of mice seem particularly resilient to the potentially adverse effects of

hyperglycaemia [44]. In contrast, human islets and islets isolated from genetically susceptible rodent species clearly display glucose toxicity manifested in defective insulin secretion [41, 45-47]. Two potentially important considerations arise from these observations. First, species differences in susceptibility might be due to differences in endogenous protection against the mechanisms involved in mediation of glucose toxicity. Secondly, the apparent requirement for a genetically susceptible B-cell might imply that the deleterious effects of hyperglycaemia may become manifest by imposing additional functional strain on existing weakspots in the insulin secretory pathway of predisposed B-cells.

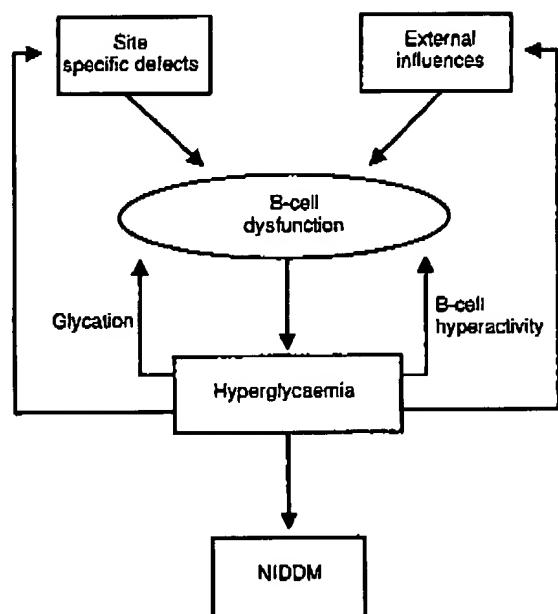
Role of glycation in B-cell glucose toxicity

Despite compelling evidence that B-cell glucose toxicity makes an important contribution to defective insulin secretion in established NIDDM, few studies have addressed the molecular mechanisms involved. A component of the glucose toxicity induced experimentally *in vivo* or *in tissue culture* may be secondary to chronic glucose-induced stimulation of B-cell hyperactivity [40, 41]. This aspect is discussed above. However, it is hard to transpose this situation to the B-cell in NIDDM, where glucose responsiveness is already compromised. With this in mind, recent studies have been conducted to assess the role of glycation of B-cell proteins in glucose toxicity and defective insulin secretion. Using the newly established glucose-responsive BRIN-BD11 cell line [48], it has been shown that detrimental effects of chronic exposure to hyperglycaemia on insulin secretory responsiveness are associated with a substantial glycation of intracellular proteins [49]. Since glycation can be expected to influence the function of key proteins in the B-cell secretory machinery, it is not unreasonable to propose that glycation of important regulatory proteins serves as a cardinal mediator of B-cell glucose toxicity. Furthermore, ongoing studies indicate that insulin is also a target for glycation in B-cells exposed to hyperglycaemia and that glycation impairs insulin-mediated glucose disposal at peripheral tissues [50, 51]. In this respect, it appears that glycation of insulin in NIDDM provides a novel link in the vicious spiral that, by promoting insulin resistance, exacerbates hyperglycaemia and consequently B-cell dysfunction.

Conclusions

Pancreatic B-cell dysfunction in NIDDM represents the combined effects of site-specific deficits in the

Figure 1
Model for interactions between site-specific defects, external influences and glucose toxicity in B-cell dysfunction and NIDDM



stimulus-secretion coupling pathway compounded by an array of diabetes-induced deleterious external influences on the B-cell (Figure 1). Studies in animals with NIDDM indicate heterogeneity in the molecular mechanisms underlying defective insulin secretion. However, growing evidence suggests that abnormalities in the early steps of B-cell glucose recognition and toxic effects of glucose mediated through glycation of B-cell proteins may be of particular importance.

The authors' research on mechanisms of pancreatic B-cell dysfunction is generously supported by the British Diabetic Association, Wellcome Trust, Department of Health and Social Services (NI) and University of Ulster Research Committee.

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Received 11 October 1993

Nitric oxide toxicity in pancreatic islet cells: role of protein biosynthesis, calcium influx and arachidonic acid metabolism

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Introduction

Nitric oxide (NO) appears to be an important mediator of the inflammatory attack against islet cells in autoimmune diabetes. The lysis of islet cells by acti-

vated macrophages *in vitro* is NO dependent [1] and can be mimicked by exposure of islet cells to chemical NO donors [2]. The lytic effect of interleukin-1 (IL-1) on islets is also mediated by NO [3]. Finally, inhibition of the β -islet cell response to glucose, by incubation with IL-1 under non-lytic conditions, requires NO synthase activity [4].

The mechanism of islet cell lysis by NO has not been elucidated. The discovery that nicotinamide protects against NO toxicity [2] and func-

Abbreviations used: NO, nitric oxide; $[Ca^{2+}]_i$, free calcium ion concentration; IL-1, interleukin-1.

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